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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,571	06/09/2000	BERNARD CALAS	19904-009	2070

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,571	CALAS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,24,29,30,32-34,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,24,29,30,32-34,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *0804*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The previous Office Action (Advisory Action) dated 9/16/04 is vacated because the Office Action mailed March 3, 2004 is not a final rejection.

Status of the Claims

2. Claims 18-20, 24, 29, 30, 32-34, 37 and 38 are pending.

Applicants' amendment filed August 27, 2004 is acknowledged, and applicants' response has been fully considered. Claims 18, 20, 24, 29, 30 and 32-34 have been amended, claims 21-23, 25, 35 and 36 have been cancelled, and new claims 37 and 38 have been added. Thus, claims 18-20, 24, 29, 30, 32-34, 37 and 38 are examined.

Objection Withdrawn

3. The previous objection to new matter added to the specification, is withdrawn in view of applicants' cancellation of the claim, applicants' amendment to the claim, and applicant's response at page 8 in the amendment filed August 27, 2004.

4. The previous objection to claim 23, is withdrawn in view of applicants' cancellation of the claim in the amendment filed August 27, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

5. The previous rejection of claims 25, 30 and 32-34 under 35 U.S.C.112, first paragraph, regarding written description, is withdrawn in view of applicants' cancellation of the claim, and applicants' amendment to the claim, and applicant's response at page 8 in the amendment filed August 27, 2004.

6. The previous rejection of claims 18-25, 29, 30 and 32-36, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' amendment to the claim, and applicants' response at page 8 of the amendment filed August 27, 2004.

Claim Objections

7. Claims 18-20, 24, 29, 30, 32-34, 37 and 38 are objected to because of the use of "SEQ. ID NO. 23". Use of "SEQ ID NO:23" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18-20, 24, 29, 30, 32-34, 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a linear peptide SEQ ID NO:23; a specific compound of formula (IV), wherein A is the amino acid sequence of SEQ ID NO:23, Z is biotin or doxorubicin, m=1 and n=0; or a method of vectoring biotin or doxorubicin to a target cell using the conjugate of biotin-peptide or doxorubicin-peptide, wherein the peptide is the amino acid sequence of SEQ ID NO:23, does not reasonably provide enablement for a moiety of a linear peptide to vectorize active sustances, wherein the moiety of the linear peptide is a fragment of SEQ ID NO:23 having at least 5 successive amino acids; a compound of formula (IV), wherein A is SEQ ID NO:23 or the fragment thereof; a pharmaceutical composition a diagnostic agent comprising the compound of formula (IV); or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a

linear peptide of SEQ ID NO:23 or the fragment thereof, wherein the active substance, the signal agent, and the target cell, cell compartment, or organ are not specifically defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-20, 24, 29, 30, 32-34, 37 and 38 are directed to a linear peptide obtained from an antibiotic peptide or a moiety of the linear peptide to vectorize active sustances, where the linear peptide comprises SEQ ID NO:23, and the moiety of the linear peptide is at least 5 successive amino acids of SEQ ID NO:23 (claims 18, 19); a compound of formula (IV) (claims 29, 30, 32, 37 and 38); a pharmaceutical composition comprising the compound of formula (IV) (claim 33); a diagnostic agent comprising the compound of formula (IV) (claim 34); or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and the linear peptide from antibiotic peptide (claims 20 and 24). The specification, however, only discloses cursory conclusions (page 8, line 19-page 13, line 7) without data supporting the findings, which state that the peptide derived from an antibiotic peptide having the formula (I) or (II), or moieties of the peptides, and a compound of formula (IV) containing the peptide, an active substance and a signal agent, can be used to vector one or more active substances for therapeutic and for diagnostic applications. There are no indicia that the present application enables the full scope in view of the linear peptide comprising SEQ ID NO:23 or moiety of the linear peptide; the compound of formula (IV), and the method vectoring an active substance using the linear peptide as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is

enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the moiety of the linear peptide; the active substance in the conjugate; and the active substance and the signal agent in compounds of formula (IV), which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification only demonstrates specific analogs of protegrin and tachyplesin (e.g., SEQ ID NO:23 and other linear peptides in Tables I and II); the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines (Tables III and IV), which were the basis for vectoring an active substance in an organism (Examples 1-4). However, there are no working examples indicating the fragments of SEQ ID NO:23 vector active substance; or a conjugate or a compound of formula (IV) containing SEQ ID NO:23 or its active fragments, an active substance and an signal agent is targeted to a specific cell or organ.

(3). The state of the prior art and relative skill of those in the art:

The related art has shown certain analogs of protegrin and tachyplesin (e.g., pages 20-22 in Lehrer *et al.* WO 96/37508), which do not have cysteines and have decreased antimicrobial activity as compared to peptides having disulfide bonds. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the vectoring effect of fragments of SEQ ID NO:23; identities of conjugates or compounds of formula (IV) containing SEQ ID NO:23 or its various fragments and various active substances; and the effect of the conjugate in vectoring an active substance to be considered enabling for all variants.

(4). Predictability or unpredictability of the art:

The specification indicates certain linear peptides in Table III (protegrin peptides including SEQ ID NO:23) and Table IV (tachyplesin peptides) have internalization ability toward certain cell lines, and it appears an increase in amphipathicity have positive effect in the protegrin family, however, the specification does not provide sufficient teaching regarding internalization ability of fragments of SEQ ID NO:23 in the conjugate or compound of formula (IV), thus it is not readily apparent that one would have been able to a priori predict the degree of internalization ability of the fragment of SEQ ID NO:23 and the vectoring effect of the conjugate containing various active substances and SEQ ID NO:23 or its fragments; or the vectoring effect of compounds of formula (IV) containing various active substances, various signal agents and SEQ ID NO:23 or its fragments.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a linear peptide comprising SEQ ID NO:23, or a moiety of the linear peptide, a compound of formula (IV), a pharmaceutical composition or a diagnostic agent comprising the compound of formula (IV), or a method of vectoring an active substance to a target cell, cell compartment, or organ using a conjugate of active substance and a linear peptide comprising SEQ ID NO:23, or its active fragments. The specification only indicates specific analogs of protegrin and tachyplesin (e.g., SEQ ID NO:23 and other linear peptides in Tables I and II); the conjugates of the peptide with doxorubicin or biotin; and the internalization abilities of these peptides in different cell lines (Tables III and IV), which were the basis for vectoring an active substance in an organism (Examples 1-4). However, the specification has not demonstrated the vectoring effects of fragments of SEQ ID NO:23, conjugates containing SEQ ID NO:23 or active fragments thereof and various active substances, or compounds of formula (IV) containing SEQ ID NO:23 or active fragments thereof, various active substance and various signal agents. There are no working examples indicating the claimed variants and associated methods except for the conjugate of biotin-peptide or doxorubicin-peptide. Since the specification fails to provide sufficient teachings on the vectoring effect of the fragments of SEQ ID NO:23 in the conjugates or compounds of formula (IV), it is necessary to have additional guidance on the identities of conjugates or compounds of formula (IV), and to carry out undue experimentation to assess the effects of linear peptides or their moieties in conjugates or compounds of formula (IV) for vectoring active substances to target cells, the experimentation is undue because further research is required to practice the claimed invention.

(6). Nature of the Invention

The scope of the claims includes many variants, but the specification does not provide sufficient teachings on the effect of the linear peptide comprising SEQ ID NO:23, or its fragments in vectoring various active substances to target cells or organs. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the guidance and the teaching in the specification are limited, the effect of the claimed compound is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the claimed variants in vectoring an active substance to a target cell or organ.

In response, applicants indicate claims have been amended and the specification is enabling for the claimed subject matter and the claimed method of vectoring, the added term "moiety of said linear peptide" is well supported by the specification (see page 9, line 28+) (pages 7-8 of the response). The response has been fully considered, however, the argument is not found persuasive because the specification only shows internalization abilities of specific peptides of protegrin and tachyplesin (e.g., SEQ ID NO:23 or other linear peptides in Tables III and IV) in different cell lines (Example 3) and the internalization of the conjugate of SM 1738 and doxorubicin (Example 4), it has not demonstrated the vectoring effects of fragments of SEQ ID NO:23; or a conjugate or a compound of formula (IV) containing SEQ ID NO:23 or its fragment is effective in vectoring a specific active substance to a specific cell compartment, cell or organ, as encompassed by the claims. Since the specification does not provide sufficient teaching on the identities and effects of the conjugates and the compounds of formula (IV), it

requires undue experimentation to practice the claimed invention. Thus the full scope of the claim is not enabled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 20, 30, 33 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 20 is indefinite because of the use of the term "target". The term cited renders the claim indefinite, is not clear to what target is intended for vectoring.

11. Claim 30 recites the limitation "the lysines of linear peptide (A)" in line 5. There is insufficient antecedent basis for this limitation in the claim because there is no lysine in peptide (A).

12. Claim 33 is indefinite because the claim recites "a pharmaceutical composition", which comprises the compound of formula (IV) as active ingredient, it is not clear what else is included in the composition as to "a pharmaceutical composition".

13. Claim 38 is indefinite because the claim recites Markush group using the closed language of "selected from the group consisting of", however, numerous chemical molecules such as undefined anti-tumorals, antivirals, anti-inflammatories and agents preventing the degradation of organs and/or tissues are included in the group.

Conclusions

14. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
December 11, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER